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VITAMIN DEFICIENCY IN NERVOUS AND MENTAL DISEASE

II. Clinical Studies

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VITAMIN DEFICIENCY IN NERVOUS AND MENTAL DISEASE

II. Clinical Studies

By **RUTH WOODS**

The recognition of the intimate relationship which exists between dietary factors, particularly the vitamins, and the nervous system has provided a new approach to problems of nervous and mental dysfunction. Basic research has established that certain vitamins are necessary for the proper functioning of the brain and spinal cord. The influence of such vitamins may be exerted in either or both of two fundamental ways: Vitamins may be required to preserve the physical integrity of brain and nerve tissue. Or they may be essential, by virtue of their close association with enzyme systems, for the maintenance of normal metabolic reactions in the central nervous system.* If either the brain itself or the intricate network of nerves which regulate body activities undergo degenerative structural changes as a result of vitamin insufficiency, there will naturally result symptoms indicative of the failure of these systems such as mental aberrations and neurologic disorders. Accumulation of the products of abnormal metabolism in the brain and spinal cord will, in a similar manner, interfere with normal functioning of these systems and thereby also result in typical mental and neurologic aberrations.

The previous issue of this *Review* has described the biochemical relationships between the B vitamins and the central nervous system. The present paper will summarize the outward clinical signs of the disturbed biochemical relationships resulting from a deficient supply of these vitamins, particularly thiamine and nicotinic acid.

Emotional and Psychological Disturbances:

Experimental Neurasthenia: The term neurasthenia is used generally to designate a minor psychiatric disturbance which is thought to be more dependent upon constitutional factors than most other mental disorders. The overall picture of neurasthenia includes states of tension, irritability, weakness, and "nervous exhaustion." There often may be associated complaints concerning the functioning of the bowels, heart, skin and genito-

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*cf. *Borden's Review of Nutrition Research*, December, 1946: "Vitamin Deficiency in Nervous and Mental Disease. I. Experimental Findings."

urinary system. The exact predisposing cause of the neurasthenia syndrome is not known. But as has been stated, factors of a physiological, constitutional nature are strongly implicated.

Neurasthenia has been produced experimentally as a result of experiments designed to observe the effects of thiamine deficiency in human volunteer subjects.* Jolliffe *et al* (1) at Bellevue Hospital in New York and Williams *et al* (2, 3, 4) at the Mayo Clinic both succeeded in producing a neurasthenic syndrome in nearly all of their thiamine-deficient subjects within a relatively short time. Jolliffe's subjects complained of fatigue, lassitude, loss of appetite, pain in the stomach, burning of the feet, marked shortness of breath on exertion, muscle cramps and palpitation. In the group at the Mayo Clinic, early signs of mental disturbance included changes in customary behavior, marked alteration of attitude and progressively decreasing ability to perform accustomed tasks or to make social adjustments within the group. All of the subjects became irritable, depressed, quarrelsome, uncooperative, fearful and suspicious.

Subjects who had never before complained, now reported unusual sensitivity to painful stimuli and to noise, insomnia, headaches, general tension, lack of appetite, nausea, reduced capacity for work or exercise. The authors point out that these signs of inefficiency and abnormalities of personality and behavior were not evident before the period of thiamine restriction, but appeared only after several weeks on the test diet. The fact that these signs all disappeared following the administration of thiamine without knowledge on the part of the patients, indicates conclusively that thiamine deficiency was responsible for the abnormal behavior.

Sebrell (5) has particularly emphasized the ease with which the early mental symptoms of thiamine deficiency may escape detection by the physician through being masked by other diseases in which it occurs as an unlooked for complication. It is not unlikely, he points out, that many cases of mental distress due to thiamine deficiency have been missed as complications of such diseases as diabetes, ulcerative colitis, peptic ulcer and chronic alcoholism.

In assessing the relationship between thiamine deficiency and the development of the neurasthenic syndrome, it is important to keep in mind that the clinical picture of neurasthenia is extremely varied and that many symptoms of the disorder occur also in apparently well-nourished persons. In such

*cf. *Borden's Review of Nutrition Research,* November, 1946: "Experimental Vitamin Deficiency in Man."

persons the symptoms of neurasthenia frequently respond to psychotherapy. As Bowman and Wortis (7) have emphasized:

> "It should therefore not be inferred that all neurasthenia is based on thiamine or other nutritional deficiency. It does, however, seem fairly certain that a syndrome possessing many of the characteristics of the ill-defined neurasthenic syndrome can be produced by nutritional deficiency. The need to isolate this group from neurasthenic syndromes of other etiology is emphasized."

Clinical Malnutrition: Confirmation of the close relationship between mental status and thiamine intake has been found in clinical observations on patients suffering from pellagra and other forms of malnutrition. It is now known that although lack of nicotinic acid is the most predominant dietary deficiency in pellagra, this disorder is actually the result of a multiple vitamin deficiency. Likewise, although it has been demonstrated that the severe psychoses of pellagra will respond to treatment with nicotinic acid, certain of the early, mild mental disturbances can be traced directly to a lack of thiamine.

Spies *et al* (6) have pointed out that symptoms which signify disturbances in the emotional behavior of a person may often occur as the only outward manifestation of a deficiency state. Such emotional disturbances respond readily to vitamin therapy. These investigators are emphatic, however, in stating that in other circumstances:

> ". . . Similar symptoms occur in persons without deficiency diseases and will not be modified by vitamin therapy. . . . Any (vitamin) therapy mentioned *(by the authors in their studies)* is recommended for emotional symptoms only when they are associated with deficiency diseases, and certainly not as a panacea for emotional disturbances in general."

At the Nutrition Clinic where thousands of patients with dietary deficiencies have been studied for a period of about ten years, a large group of persons complaining of emotional disturbances was selected for observation. None of these presented clinical evidence of thiamine deficiency (beriberi) in that there was no involvement of the heart or of the peripheral nerves. Yet all of these patients presented mental disturbances which the investigators had come to associate with their typical thiamine deficiency cases. Although diagnostic signs were not yet apparent, analyses of the diets and the mental symptoms strongly suggested the existence of early thiamine deficiency. This was confirmed by the favorable response to thiamine administered without knowledge on the part of the patients.

The emotional abnormalities most frequently encountered were fear, apprehension, irritability, anger, hostility, depression, extreme sensitivity,

"simple anxiety states" and progressively severe conditions extending into "anxiety neuroses or anxiety hysteria."

In addition to the emotional disturbances, almost all of the patients complained of poor memory and difficulty in concentration. They forgot where they put objects. They told the same incidents over and over. They would start on errands and forget where they were going.

The response of most of these conditions to thiamine was phenomenal. In the words of the authors:

> "The intravenous administration of 50 mg. of thiamine* produced a truly amazing change in personality within from 30 minutes to 20 hours; a transformation from a timid, apprehensive, shrinking, fearful, depressed, unreasonable, uncooperative person to a smiling, pleasant, friendly, cooperative, happy human being. Every patient in whom there was conclusive evidence of deficiency disease with emotional disturbances showed an amelioration of these symptoms and a return to a more nearly normal emotional and intellectual state following thiamine therapy. In no case was there similar improvement after saline injection.†"

The clinical findings of disturbed mental and emotional reactions have been interpreted as an indication of an abnormal functioning of the brain cortex. The cortical cells are believed to be the seat of intellectual integration — the combination of nerve stimuli into behavior patterns, associations, and interpretation in terms of past experiences. From the experimental studies described in the preceding issue of this *Review,* it is easy to visualize a tie-up between thiamine deficiency and the integrity of the brain cortex which would result in the clinical manifestations described.

Spies *et al* emphasize, however, that one has to keep in mind that similar emotional disturbances are seen in patients with psychoneuroses in which there is as yet no evidence‡ of disturbed cortical metabolism or structure. They report that some of their malnourished patients had evidence of a neurotic background previous to their illness, and suggest that in such cases the combination of a deficiency state and a "fertile soil" led to the emotional disturbances. On the other hand, they suggest that what might have been considered "neurotic traits" in childhood (temper tantrums, sleep-walking, bed-wetting, nightmares and behavior problems) may, in these patients, have actually been due in part to an early nutritional deficiency state. The fact remains, however, that all of their subjects, regardless of previous mental condition or environmental stress, responded promptly to vitamin

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*Equivalent to more than 25 times the average recommended daily allowance.

†Saline injections were given instead of vitamin injections as a means of checking psychological response to supposed vitamin therapy.

‡As reflected by electroencephalograph (brain wave) studies.

therapy. This they cite as an illustration of the important role which an adequate nutritional status plays in maintaining a well-integrated personality.

Neurological Disturbances:

Polyneuritis: Multiple neuritis or polyneuritis is a broad general term describing certain degenerative nerve changes occurring in the nerves of the extremities (peripheral neuritis). There are many forms of this neurological disease and as many causes, many of which are infectious or toxic in nature.* With the discovery in the Orient that beriberi is a nutritional deficiency disease, the typical polyneuritis of beriberi was differentiated from the infectious forms of polyneuritis as a neuritis of nutritional origin. Not until many years later was it realized that many forms of multiple neuritis in the Western Hemisphere, where typical beriberi is rather uncommon, are actually nutritional polyneuritis. It soon became apparent that the polyneuritis frequently associated with pregnancy, the polyneuritis of chronic alcoholism, and the polyneuritis accompanying gastrointestinal diseases had one factor in common with each other and with the polyneuritis of beriberi: A deficiency of the vitamin B complex, particularly thiamine.†

(Predisposing Causes): Although in the Orient polyneuritis develops as a result of dietary inadequacy alone, this is generally rare in the Western Hemisphere. The vitamin deficiency usually is brought about indirectly by factors which interfere with efficient absorption and assimilation, or which heighten the normal requirement, usually in combination with a decreased food intake. For example, in chronic alcoholism appetite and food intake are lessened while there may be an increased need for thiamine to handle the additional calories provided by alcohol; in pregnancy complicated by severe vomiting there is considerable loss of food which, combined with the already heightened food requirements and decreased appetite is equivalent to a sharply diminished food intake; gastrointestinal disorders, particularly those characterized by chronic diarrheas (bacterial or parasitic infections, sprue, ulcerative or mucous colitis), cause interference with food absorption as well as excessive loss of nutrients in the stools; fevers, hyperthyroidism and prolonged strenuous physical activity markedly raise the requirement for food factors, particularly vitamins; the highly restricted diets necessary in certain illnesses are usually deficient in vital food factors. Unless treatment in these conditions includes vitamin therapy as well as the specific

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*These include infectious polyneuritis, diphtheritic polyneuritis, lead and arsenic poisoning polyneuritis, etc.

†Because it was originally believed that thiamine was the sole factor in polyneuritis, it was frequently referred to as the "anti-neuritic" vitamin. British scientific literature still includes the synonym "aneurin" for thiamine.

treatment for the disease, nutritional failure leading to polyneuritis is inevitable.

(Manifestations of Nutritional Polyneuritis): Nutritional polyneuritis is usually slow and insidious in its development. The earliest signs may be a heaviness of the legs and tenderness of the calf muscles when squeezed. Long walks result in undue weakness, the legs suddenly collapsing after some distance. The distances which may be walked before this collapse occurs are gradually shortened until the patient finds he can walk only a hundred feet or so. Burning of the soles of the feet and numbness appear next. There is a diminished power in flexing the toes and the knee and ankle reflexes gradually disappear. An increased sensitivity to pain occurs up the leg, developing finally into numbness and complete loss of sensation. Similar changes follow later in the upper extremities. Mental symptoms may sometimes complicate the picture resulting in the disturbance known as Korsakoff's syndrome.

The disease can be arrested and cured by adequate supplementation of the diet with thiamine and other members of the vitamin B complex. Polyneuritis has been induced experimentally by Williams *et al* (8) in one of their studies on human thiamine deficiency, thereby resolving a long-existing debate as to the significance of thiamine in the cause of this disease.*

Parkinson's Disease: The neurological disease described as Parkinsonism, is a serious disorder characterized by uncontrollable muscular spasms or palsy, muscular weakness, and progressive loss of muscular coordination. There have been scattered reports on the successful use of pyridoxine (vitamin B_6) in the early stages of this disease, but conclusive evidence as to the mode of action or actual efficacy of this vitamin await more extensive clinical experience.†

Psychiatric Disorders:

Psychosis of Pellagra: The mental and neurological symptoms of pellagra were recognized centuries ago by the very earliest observers of the disease. It was not until a few years ago, however, that the multiple vitamin deficiency origin of these manifestations was recognized. Many of the neurological disturbances and most of the early mental symptoms of neurasthenia have been traced to thiamine deficiency. Certain of the later, more severe psychotic

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**cf. Borden's Review of Nutrition Research,* November, 1946: "Experimental Vitamin Deficiency in Man."

†This subject has been discussed in the preceding issue of *Borden's Review of Nutrition Research,* "Vitamin Deficiency in Nervous and Mental Disease. I. Experimental Findings."

manifestations, however, seem to be specific evidence of nicotinic acid deficiency. Following the neurasthenia, Spies *et al* (9) note the development of a psychosis characterized by loss of memory, disorientation,* confusion and confabulation† associated with mania, depression, delirium or delusions of persecution. Reports from Bellevue (10, 11) indicate that the latter symptom (described as paranoid reactions) is quite common in pellagrins. Although Spies *et al* report recovery of their psychotic cases upon adequate vitamin therapy, Wortis (10) points out that careful psychiatric examination of cases of longer duration reveals that these patients are often left with residual organic memory defects (Korsakoff syndrome). If the psychosis is of very long standing, however, nicotinic acid therapy may be of little or no benefit. This does not imply that the illness was not caused by nicotinic acid deficiency. Rather, the metabolic changes have progressed to irreversible structural changes. Again, it must be pointed out that the psychotic symptoms may not always be due to nutritional deficiency alone. There must be evaluation of the symptoms in order to determine the proper therapy.

Nicotinic Acid Deficiency Encephalopathy: In 1939, Cleckley and Coworkers (12) reported the dramatic response of 19 patients in comatose or stuporous states to nicotinic acid, although no signs of pellagra were present. The following year, Jolliffe *et al* (13) reported 150 cases of a newly recognized degenerative brain disease or encephalopathy which showed some similarity to the cases observed by Cleckley and other earlier workers. The disease is apparently an unusual manifestation of nicotinic acid deficiency in which there are none of the ordinary signs of pellagra, but merely severe mental and neurological changes. The encephalopathic disease was found to occur either as the only manifestation of a deficiency disease or in conjunction with typical pellagra, the polyneuritis of thiamine deficiency, or with certain symptoms of the Wernicke syndrome. The disease is characterized by clouding of consciousness, cog-wheel rigidities of the extremities and uncontrollable sucking and grasping reflexes. Some of these symptoms are similar to, and must be differentiated from those occurring during delirium tremens, the delirium of infectious diseases and other brain disturbances.

Patients with this type of encephalopathy when treated by hydration plus thiamine almost invariably die (95 per cent). Those treated by hydration plus the entire B complex show a moderate drop in mortality (50 per cent). Those treated by hydration plus nicotinic acid exhibit only 15 per

*Confusion as to time, place or identity.
†The recital of experiences or giving of ready answers without regard to truth.

cent mortality. Cures, however, again are not entirely complete. Marked organic memory defects usually remain with the patient.

Wernicke's Syndrome: The neuropsychiatric disease known as Wernicke's syndrome was first described in 1881 by Karl Wernicke (14). It consists of a clouding of consciousness, loss of motor control and paralysis of the eye muscles. Wernicke's disease occurs most frequently in chronic alcoholism, but has also been observed in non-alcoholic patients suffering from gastrointestinal disorders, severe vomiting or refusal to eat. For this reason, the early theories implicating alcohol as the cause of Wernicke's disease were discarded. The possibility of a metabolic origin of the disease was considered. In 1938, the experimental production in pigeons on a thiamine-deficient diet of a brain disease with a tissue pathology identical with that seen in Wernicke's syndrome provided the first confirmation of the nutritional deficiency nature of this disease (15). Further confirmation followed with the discovery of Chastek paralysis in foxes reared on raw fish diets. Chastek paralysis, the animal counterpart of Wernicke's syndrome, was eventually traced to a thiamine deficiency resulting from the destruction of dietary thiamine by an enzyme present in raw fish.

Jolliffe, Wortis *et al* (16, 17) in studies on more than 30 cases conclude that Wernicke's syndrome is probably a combination of several nutritional deficiencies, principally thiamine deficiency, affecting the nervous system. They find that the eye paralysis responds to thiamine therapy. The clouding of consciousness may be attributed to any number of factors which interfere with brain metabolism. These include, among others, lack of carbohydrate, lack of oxygen, lack of thiamine, nicotinic acid or riboflavin. Little is known as yet with respect to the cause or therapy for the difficulty in muscular coordination.

The investigators at Bellevue report further interesting observations on this disease. They note, for example, that other deficiency conditions (pellagra, nicotinic acid deficiency encephalopathy, riboflavin deficiency, scurvy) may and often do superimpose themselves on the characteristic Wernicke symptoms. Further, they have observed that the symptoms of eye paralysis are almost always accompanied or preceded by the polyneuritis of thiamine deficiency, again confirming the close association between the disease and nutritional deficiency.

All patients who received adequate vitamin therapy recovered. Unfortunately the recoveries are usually complicated by the development of a Korsakoff syndrome which, to date, has shown only a variable response to

further vitamin therapy. Chemical studies yield additional proof of the vitamin deficiency nature of the disease. In a study of eleven patients with Wernicke's disease, blood tests revealed abnormally high levels of pyruvic acid in all of the subjects (18).* On the other hand, in a study of 280 cases of various neuropsychiatric and medical disorders unassociated with any clinical evidence of thiamine deficiency, all but one showed completely normal blood levels of pyruvic acid (19). Following the administration of thiamine, these levels returned to normal and clinical improvement (clearing of the mental status and of the vision) was noted (16, 18). The authors point out, however, that the Wernicke syndrome as seen clinically does not represent a simple thiamine deficiency but is often associated with a lack of other nutritional factors as well. They therefore advise treatment with a high-calorie, multi-vitamin-rich diet in addition to thiamine.

Korsakoff Syndrome: The Korsakoff syndrome, first described by the Russian psychiatrist in 1887 (20) consists of a defective memory for recent events, with a tendency to give ready, but meaningless or untrue answers to questions and a confusion in identifying time sequences, places or persons. It is a frequent residual complication of recovered cases of pellagra psychosis, nicotinic acid encephalopathy and Wernicke's disease. It also occurs as a co-existing disturbance in chronic alcoholism and many other diseases. Because peripheral neuritis is often a part of the Korsakoff syndrome, thiamine deficiency has frequently been suggested as the predisposing cause. Results reported by various investigators, however, are so conflicting as to cast considerable doubt upon the efficacy of thiamine in the treatment of this disorder. In general it is believed that only certain cases of Korsakoff's syndrome may result from nutritional disturbances, particularly those associated with alcoholism. Because of the variable response to thiamine therapy, many more controlled studies will be required before a true evaluation can be made of the role of this vitamin in the cause and treatment of the disorder.

Alcoholism and Delirium Tremens: The effect of alcohol on the brain and nervous system has been a matter of intensive investigation for many years. There is little direct information as to the specific pathways involved or even as to whether alcohol *per se* is responsible for most of the damage observed. The group at Bellevue (21, 22), however, has expressed the opinion that the cerebral complications of chronic alcoholism are more probably due to a metabolic disturbance (specifically avitaminosis) than to the direct toxic

*Evidence of thiamine deficiency, *cf. Borden's Review of Nutrition Research,* December, 1946: "Vitamin Deficiency in Nervous and Mental Disease. I. Experimental Findings."

action of alcohol in the nervous system. In support of this theory they point out that many of the deficiency diseases affecting the nervous system occur in alcohol addicts. Vitamin-free alcohol is often substituted for foods. Impaired gastrointestinal absorption is common in alcoholism because of associated liver and stomach disorders. This leads to inefficient utilization of whatever small amount of food is eaten. Finally, alcoholic states, particularly delirium tremens, result in an increase in metabolism which, in turn, heightens the requirement for vitamins and other dietary essentials. This may often precipitate deficiencies which might otherwise not develop.

The evidence for nutritional deficiency in delirium tremens is very strong. In addition to the facts just cited, tests almost always reveal a low vitamin C content of the blood and spinal fluid; signs of peripheral neuritis in about 30 per cent of the cases; evidence of pellagra, scurvy and of riboflavin deficiency. There have been conflicting reports in the literature with respect to the value of thiamine and nicotinic acid in treating tremens, despite the fact that neurological deficiency diseases associated with a deficiency of these vitamins are fairly common complications of the condition (9, 23, 24, 25, 26, 27).

The great complexity of this problem is demonstrated in an interesting report by Wortis (28) on four patients with delirium tremens. These patients were treated with glucose and saline, and kept on a diet markedly inadequate in the entire vitamin B complex. Two recovered promptly. The third patient developed a typical nicotinic acid deficiency encephalopathy and the fourth developed a typical Wernicke syndrome. The third patient required intravenous medication with nicotinic acid and the fourth intravenous administration of thiamine and other vitamins before recovery took place.*

Wortis comments:

> "Before treatment was instituted we could see no essential difference in the condition of these patients or in the degree of involvement. We have repeatedly observed this phenomenon in patients who, admitted to the hospital with delirium tremens, develop other types of encephalopathy requiring specific treatment before recovery sets in.
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> "It seems, therefore, that deficiency of thiamine and nicotinic acid is not specific in the causation of delirium tremens, and that administration of these vitamins is not specific in its treatment. We believe, however, that delirium tremens is a factor of considerable importance in producing other types of nutritional encephalopathy (nicotinic acid deficiency encephalopathy; Wernicke's syndrome,

*Recovery in the fourth case was accompanied by a residual Korsakoff psychosis which showed no further response to thiamine therapy.

etc.). The delirium, with its marked increase in psychomotor activity, so raises the metabolic requirements of the individual that clinically latent deficiency states may become manifest. If then an individual nearly depleted of thiamine or nicotinic acid develops delirium tremens, he is very apt to develop complicating syndromes. It is this type of patient, we believe, who is materially helped by the addition of thiamine and nicotinic acid to his therapeutic regimen."

Other Neurological Disorders: Various vitamins have been recommended for such conditions as neuralgia of the face, sciatica, migraine, auditory nerve deafness, St. Vitus' dance, muscular dystrophy*, amyotrophic lateral sclerosis and senile psychosis. To date, the evidence is not sufficiently conclusive to demonstrate a definite relationship, if any, between the various vitamins and these diseases. Nevertheless, studies along these lines are still in progress and hold forth much promise for the future.

**cf. Borden's Review of Nutrition Research,* September, 1945: "Vitamin E in Veterinary and Clinical Medicine."

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